

APPLICANT(S): DALTON, James T.  
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### **REMARKS**

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

### **Status of Claims**

Claims 1-9, 12-23, 27-34, 36-67, 69-78 and 80-95 are currently pending in the application. Claims 21-23, 32-34, 38-51, 65-67, 76-78 and 82-95 have been withdrawn from consideration. Claims 25 and 26 have been cancelled. Claims 10, 11, 24, 35, 68 and 79 have been cancelled in a previous response. Claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 have been rejected. Applicants note that claims 53-94 were correctly renumbered as claims 54-95 in the response filed November 24, 2008. Applicants also note that the Advisory Action mailed December 22, 2008 does not indicate that claims 12-20 have been rejected. However, based on the Examiner's comments in Section 11 of the Advisory Action, Applicants assume that the rejection of these claims has been maintained.

### **CLAIM REJECTIONS**

#### **Double Patenting Rejections**

In the Office Action, the Examiner rejected claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-85 of U.S. Patent No. 6,838,484 or over claims 1-10 of U.S. Patent No. 6,569,896 or over claims 1-5 of U.S. Patent No. 6,492,554. Applicants respectfully disagree.

Applicants are hereby requesting the rejections be held in abeyance until such time as allowable claims are identified.

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### 35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 under 35 U.S.C. § 103(a), as allegedly being obvious in view of the combined teaching of Tucker (U.S. Patent No 4,636,505) and Miller *et al.* (WO 98/55153).

Claim 25 and 26 have been cancelled, rendering the rejection of these claims moot.

In the Final Office Action mailed March 28, 2008, the Examiner asserts that "Tucker is expressly teaching the equivalence of O-bridged compound[s] and S-bridged compounds, see column 9." In the Advisory Action mailed December 22, 2008, the Examiner further asserts that Tucker "has made compounds with both O and S and with similar properties." Thus, the Examiner alleges an equivalence between O- and S-bridged SARM compounds, and thus an equivalence between metabolites of these compounds. Applicants respectfully disagree.

Firstly, claims 1-9, 12-23, 27-34, 36-67, 71-78 and 80-95 of the present application are directed to metabolites of SARM compounds in which the SARM contains a phenyl ring substituted by an acetamido or trifluoroacetamido group (see the definition of substituent Q in claim 1). In contrast, none of the compounds recited in the Table at column 9 of Tucker contain a phenyl ring substituted with an acetamido or trifluoroacetamido group. Even in the broadest disclosure, Tucker does not teach or suggest an O-bridged SARM containing a phenyl ring substituted by an acetamido or trifluoroacetamido group. *See* the definition of R<sup>7</sup> at column 2, lines 3-24 of Tucker. Therefore, Tucker cannot teach or suggest the presently claimed metabolites of acetamido or trifluoroacetamido substituted O-bridged SARM compounds and therefore cannot render obvious claims 1-9, 12-23, 27-34, 36-67, 71-78 and 80-95.

Secondly, claims 69 and 70 of the present application are directed to hydroxylated or aminated metabolites of O-bridged SARM compounds in which the SARM contains an A phenyl ring substituted by trifluoromethyl and nitro substituents at the 3- and 4-positions, respectively, and a B phenyl ring substituted by a fluoro substituent at the 4-position. In contrast, none of the Tucker compounds contain this specific substitution pattern. Indeed, at

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col. 3, lines 56-66, Tucker discloses that preferred acylanilides include compounds that may contain seven different options for R<sup>1</sup>, four different options for R<sup>2</sup>, two different options for R<sup>6</sup>, three different options for A<sup>1</sup>, 2 different options for A<sup>2</sup> and multiple options for R<sup>7</sup>. Thus, the Tucker disclosure at col. 3, lines 56-66, is a genus of compounds that encompasses dozens of compounds. Applicants note that the only two specific O-bridged compounds disclosed by Tucker (see col. 9, lines 34 and 35) are unsubstituted at the B phenyl ring. Thus, Tucker does not teach or suggest O-bridged SARMs containing an A phenyl ring substituted by trifluoromethyl and nitro substituents at the 3- and 4-positions, respectively, and a B phenyl ring substituted by a fluoro substituent at the 4-position. Therefore, Tucker cannot teach or suggest the presently claimed hydroxylated or aminated metabolites of the O-bridged SARM compounds of subject claims 69 and 70, and therefore cannot render obvious claims 69 and 70. For at least these reasons, Applicants respectfully request that the rejection be withdrawn.

Moreover, Applicants maintain that the Examiner's assertion that Tucker teaches O- and S-substituted compounds have similar properties is incorrect. Contrary to the Examiner's assertion, Tucker fails to clearly and unequivocally teach the equivalence of O- and S-bridged compounds. The only property expressly disclosed for the compounds at column 9, Example 2 of Tucker is the physical property of melting point and in this there is a wide range, including compounds present as a gum. No where in Example 2 does Tucker describe, recognize, suggest or lay the foundation for the equivalence of activity of the group of compounds listed in Example 2. Thus, Tucker does not teach or suggest equivalent compounds with those of the subject application and hence, does not teach or suggest equivalent metabolites.

In the Advisory Action mailed December 22, 2008, the Examiner asserts that "once the [Tucker] compound is administered, *in vivo*, they are automatically changed to the metabolites, absent evidence to the contrary." (emphasis added) Even assuming, *in arguendo*, that Tucker teaches O- and S-bridged compounds have similar physical properties (which is, in fact, not the case, as outlined above with respect to melting point), this does not necessarily mean O- and S-bridged compounds are metabolized *in-vivo* in an identical manner, or that metabolites of O- and S-bridged compounds will possess similar *in-vivo* activity. Indeed,

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Applicants have provided evidence to the contrary, showing that the metabolism of O-bridged compounds is substantially different to the metabolism of S-bridged compounds (such as bicalutamide) of Tucker. Specifically, Example 5 of the present application clearly demonstrates that S-bridged bicalutamide is metabolically different from the presently claimed O-bridged SARM compounds. Upon metabolism, bicalutamide is converted from exhibiting agonist to antagonist activity, due to oxidation of the thioether linkage to a sulfonyl linkage. In contrast to the Tucker compounds, the metabolites of the SARM compounds of formulas I-IV and VII-X of the present invention contain an ether linkage, and therefore oxidation does not occur at this labile site. Rather, the major metabolites in dogs of Compound IV, for example, is the nitro-reduced product and the deacetylated product. The major metabolite of Compound III is the hydroxylated product.

Tucker does not describe or provide any foundation for the role of the O-bridged moiety, which imparts unique characteristics to the SARM compounds of the claims during metabolism, as described above. Tucker certainly provides no teaching or suggestion of metabolites of such compounds. Thus, based on the disclosure of Tucker, one of ordinary skill in the art would not have arrived at the presently claimed metabolites of O-bridged SARM compounds. Accordingly, Tucker does not render obvious the present claims.

The disclosure of Miller does not cure the deficiencies of Tucker. As is the case with Tucker, none of the specific compounds recited in Miller contain a phenyl ring substituted with an acetamido or trifluoroacetamido group (as required by claims 1-9, 12-23, 27-34, 36-67, 71-78 and 80-95). Even in the broadest disclosure, Miller also does not teach or suggest an O-bridged SARM containing a phenyl ring substituted by an acetamido or trifluoroacetamido group. See the definition of R<sup>7</sup> at page 7, lines 7-18 of Miller. In addition, none of the specific compounds recited in Miller contain an A phenyl ring substituted by trifluoromethyl and nitro substituents at the 3- and 4-positions, respectively, and a B phenyl ring substituted by a fluoro substituent at the 4-position (as required by claims 69 and 70). Therefore, Miller does not teach or suggest the SARM compounds of the subject claims, and therefore, cannot teach or suggest the presently claimed metabolites of such compounds.

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Further, Miller provides no guidance or disclosure regarding identity of metabolites of the compounds disclosed therein. Indeed, Miller explicitly negates any knowledge of *in-vivo* metabolites, stating: "[n]othing is known about the *in vivo* metabolism and pharmacokinetics of compounds of the present invention. It is **hypothesized** that they are likely to undergo *in vivo* disposition like bicalutamide and flutamide." See page 42, lines 24-27 of Miller (emphasis added). In fact, Miller's hypothesis (i.e., the oxidation of a thioether linkage to a sulfonyl linkage of bicalutamide) actually *teaches away* from the presently claimed metabolites of O-bridged SARM compounds of formulas I, II, III, IV, VII, VIII, IX and X, as these compounds possess an ether linkage and are therefore not oxidized at the corresponding site in the molecule. Moreover, Miller teaches that metabolites of the S-bridged SARMS such as bicalutamide are not even present in a time scale relevant to activities being measured *in vivo* and therefore "contribute little ... during *in vivo* studies." See page 42, lines 27-31 of Miller (emphasis added). Thus, the teachings of Miller contest the Examiner's assertion that Miller renders obvious the presently claimed metabolites due to the "simple biological phenomenon, which, is conversion of any substance *in-vivo* which have [sic] to be converted to various derivatives, absent evidence to the contrary".

Tucker and Miller, when taken alone or in combination, fail to teach, suggest or lead one skilled in the art to the O-bridged SARM metabolites of the subject claims, and therefore do not render obvious any of the present claims. Applicants respectfully request reconsideration and withdrawal of the rejection.

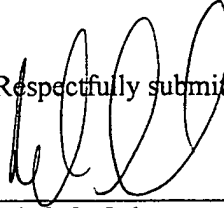
In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

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Respectfully submitted,



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